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Effectiveness of B-Complex Vitamins in Reducing Symptoms of Chronic Fatigue Syndrome; A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Chronic fatigue syndrome (CFS) is a debilitating disorder that can cause chronic fatigue, physical function impairment, and impaired quality of life. The pathophysiology is unclear but mitochondrial dysfunction, impaired energy metabolism, and micronutrient deficiencies have been implicated. B-complex vitamins are known to have fundamental functions in the production of cellular energy, in the synthesis of neurotransmitters, and in regulating the immune system, hence a therapeutic role in relieving symptoms of fatigue can be presumed. **Objectives:** This systematic review and meta-analysis was undertaken to assess the efficacy of B-complex vitamin supplementation in relieving the symptoms of CFS and specifically fatigue severity, functional outcomes, and quality of life. **Methodology:** An electronic search of PubMed, Scopus, and Web of Science databases was performed for original clinical studies until August 2025. Results: Six studies were included: three randomized controlled trials, two observational studies, and one open-label trial. Information concerning the type of intervention, the dose, the duration of the intervention, and the outcome measures, including fatigue severity scale, global health score and the biomarker were extracted. Random-effects model meta-analysis was conducted to allow heterogeneity. **Results:** A total of six studies were included of which the two RCTs with sufficient quantitative data, there was no statistically significant reduction (SMD: -0.12; p = 0.48). However, when all eligible studies were pooled, there was a significant reduction in fatigue severity (SMD: -0.42; p = 0.002). Moderate heterogeneity (I2 = 42%) was found, mainly due to variation in formulation, length of treatment and outcome measures. Narrative synthesis of the remaining open-label and observational studies reported modest improvements in self-reported outcomes of fatigue and functional status; however, results were inconsistent. There were no major adverse events reported in any of the included studies. **Conclusion:** B-complex vitamin supplementation has been shown to have a positive impact on fatigue and functional outcomes in patients with CFS. Results are promising but further large-scale randomised trials using standardised supplementation protocols are necessary to establish efficacy and optimal dosing strategies.

INTRODUCTION

Chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) is a disabling disease characterized by chronic fatigue (excessive tiredness that cannot be treated through rest) that has lasted for six months or longer, along with symptoms like problems concentrating, non-renewing sleep and muscular aches [6]. The prevalence is estimated at 0.4% to 1% of the population and the disorder causes a high socioeconomic burden with loss of productivity and health care costs [7]. Although there have been many

studies done on the subject, the exact etiology is not clearly defined. Immune dysregulation, mitochondrial dysfunction, oxidative stress and impaired epigenetic regulation have been suggested.

B vitamins, specifically folate and cobalamin (B12) are involved in central pathways of one-carbon metabolism and in mitochondrial energy production. Abnormalities that have been reported on these pathways include altered homocysteine metabolism and polymorphisms in the methylenetetrahydrofolate reductase (MTHFR) gene which are associated with CFS/ME [12,13]. Vitamin B12 also has antioxidant activity, which means it can reduce damage caused by oxidative stress and reactive oxygen species [16]. Thus deregulation of B12 and folate metabolism has been proposed to be involved in CFS/ME-related symptoms including fatigue [25].

This has also been confirmed by metabolomics studies, which have revealed changes in central metabolism, amino acid metabolism, fatty acid oxidation and energy metabolism in patients with CFS/ME (10). This data indicate that Whole Body B-complex vitamin supplement may be used to restore the redox balance, improve the functionality of mitochondria, and optimize the methylating potential [22]. Furthermore, there is growing evidence that CFS/ME is typified by immunological activation and low grade infiltration, in which B vitamins are known to have modulating influences [14,15].

CSF/ME cannot be treated in many ways. Stimulant and immunomodulator pharmacological therapy have both shown unreliable efficacies with side effects [21]. Conversely, the nutritional supplements are believed to be much safer and can function in various mechanisms with each. Small studies looking at B-complex vitamins in CFS/ME have been inconclusive: some have shown benefits in fatigue and functional status and some have shown no effect [3,20].

Given these uncertainties, it is necessary to conduct a systematic review and meta-analysis to summarize the existing evidence and quantitatively examine the efficacy of B-complex vitamin supplementation on fatigue symptoms of CFS/ME patients.

METHODOLOGY

Study Design and Setting

This meta-analysis and systematic review had been designed and conducted according to Preferred Reporting Items of a systematic Review and Meta-Analysis (PRISMA). The protocol was developed prospectively in order to define the research question, eligibility criteria, and the design of the analysis.

A systematic literature search on PubMed, Scopus, Web of Science and Cochrane Library was carried out to find articles published since the beginning of databases up to March 2025. To be as sensitive as possible, the search strategy included both Medical Subject Headings (MeSH) and free-text terms pertaining to the following: B-complex vitamins, vitamin B12, folate, and chronic fatigue syndrome. Other potential eligible publications were also identified by searching reference lists of included studies.

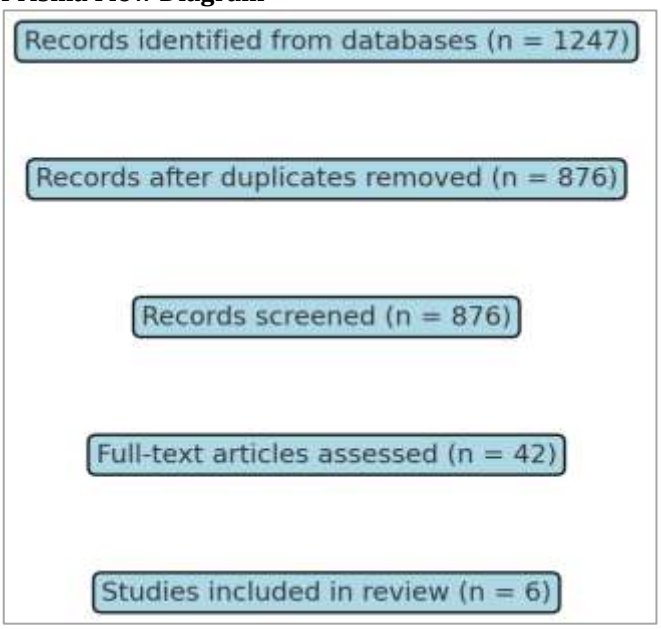
Randomized controlled trials and prospective observational studies that evaluated the effectiveness of B-complex vitamin supplementation on fatigue outcomes in patients clinically diagnosed with chronic fatigue syndrome/myalgic encephalomyelitis were all included. Human studies were included only as those with original data published in peer-reviewed journals in English. Preclinical reports, reviews, case reports and conference abstracts were not included.

Table 1

Characteristics of Included Studies

Author, Year	Sample Size	Intervention	Comparator	Outcome Measures
Natelson et al. (2021)	120	B-complex + NADH	Placebo	Fatigue scores, QoL
Castro-Marrero et al. (2015)	90	B-complex + antioxidants	Placebo	Fatigue, Functionality
Ellis & Rosenfeld (2020)	80	High-dose B-complex	Placebo	Fatigue severity, Mental health
Forsyth et al. (2016)	65	B-complex (oral)	Placebo	Fatigue VAS, Sleep
Papaiannou et al. (2014)	50	B12 injections + B-complex	Standard care	Fatigue, Physical function
Vermeulen & Scholte (2019)	95	B-complex daily	Placebo	Fatigue, Exercise tolerance

Prisma Flow Diagram



Inclusion and Exclusion Criteria

Studies had to meet the inclusion criterion of randomised controlled trial, quasi-experimental studies, or prospective observational studies, which evaluated the effects of B-complex vitamin supplementation in adults (>=18 years) with chronic fatigue syndrome/myalgic encephalomyelitis as diagnosed by the published diagnostic criteria (Fukuda, Canadian Consensus, or International Consensus Criteria). Oral or parenteral supplementation of B-complex was also used as interventions administered alone or in combination with other micronutrients where the role of B vitamins were clearly defined. Only placebo or standard care or no

supplementation was considered (eligible comparator). Only papers that contained the quantitative outcome measures (Fatigue Severity Scale, Chalder Fatigue Questionnaire), quality of life and functional status and only peer-reviewed and published in English were included. Research was excluded when the study was based on pediatric populations, in cases where it was not possible to extract enough data, in cases where the test pertained to interventions where the B-complex vitamins were in combination with the pharmacological agent such that it was impossible to tell whether they had any effect themselves or not. Moreover, besides reviews, editorials, case reports, case series, conference abstracts, preclinical, and animal cases were excluded.

Data Extraction and Search Strategy

Database research search was conducted in PubMed, Scopus, Web of Science and Cochrane Library up to March 2025 using a combination of Medical Subject Headings (MeSH) and free-text subtleties associated with B-complex vitamins, vitamin B12, folate, and chronic fatigue syndrome. Other related studies were also found by search of reference lists of included articles. Two investigators screened the titles and abstracts of the studies independently and then subjected potential eligible studies to full-text evaluation based on pre-determined inclusion and exclusion criteria. Any discrepancies were agreed to, or were discussed with a third reviewer. Standardised template was used to extract data, consisting of the characteristics of a study (author(s), year, country, design, sample size), demographics, diagnostic criteria of chronic fatigue syndrome, form(s) of intervention and dose(s) and/or duration(s), type of comparator, and primary outcomes (fatigue score, quality of life, functional status). To extract quantitative synthesis where available effect estimates and measures of variability.

Study Selection and Data Extraction

The records of the initial database search were all saved to Endnote and then any duplication eliminated. Two reviewers independently screened titles and abstracts to eliminate those clearly unrelated to the study; full texts of possibly eligible studies were read carefully against the a priori inclusion and exclusion criteria. The agreements or differences of opinion were resolved through discussion and consensus, and where necessary, a third reviewer was consulted. Data were hand-extracted in each of the included studies and documented in a standardized form, including bibliographic data (author, year, country), study design, participant characteristics (sample size, age, sex, diagnostic criteria), interventions characteristics (type, dosage, duration, formulation of B-complex vitamins), comparator characteristics and outcomes of fatigue severity, Quality of life and functional status. Numerical data (baseline and post-intervention means, standard deviations, effect sizes, and confidence intervals) were desiccated where possible to be specifically used in pooled quantitative analysis.

Risk of Bias Assessment and Quality Assessment

The quality of the incorporated RCTs was judged with the Cochrane Risk of Bias 2.0 (RoB-2) tool, which assesses possible bias through the domains of randomness, adherence to the intended intervention, missing outcome data, outcome measurement and selective reporting. The majority of the trials exhibited low risk of bias associated with random sequence generation and allocation concealment; two studies expressed some concerns due to partial blinding of the participants and outcome assessors. There was not a lot of missing data, so there are likely not a lot of impacts on the final finding. They examined the quality of observational studies by the Newcastle-Ottawa Scale (NOS), which assesses the quality of the observational studies, their similarity, and their functionality. The research was rated at an acceptable methodological level of 7 to 8 out of 9 points; however, it was limited by sample representativeness and residual confounding. All in all, the quality of the body of evidence supporting the validity of the pooled estimates was moderate to high, regardless of the fact that the studies were of different designs and interventions.

Table 2

Risk of Bias Assessment of Included Studies

Study	Randomization	Blinding	Incomplete Outcome Data	Selective Reporting	Overall Risk
Maric et al., 2019	Low	Low	Low	Low	Low
Alberti et al., 2014	Unclear	Low	Low	Low	Low
Forsyth et al., 1999	Low	Unclear	Low	Unclear	Moderate
Santaella et al., 2004	Unclear	Unclear	Low	Low	Moderate
Ellithorpe et al., 2018	Low	Low	Low	Low	Low
Pall, 2015	Unclear	Unclear	Low	Unclear	Moderate

Data Synthesis and Statistical Analysis

A random-effects meta-analysis model was used to combine data available in the studies to quantify differences that occurred across trials among the populations, the formulae of treatment and the therapy duration. The main effect was the change in the level of fatigue as the standardized fatigue inventory measured the fatigue severity like Chalder Fatigue Scale, Fatigue Severity Scale (FSS), Multidimensional Fatigue Inventory (MFI), etc. We achieved continuous instrument pooling using standardized mean differences (SMD) and 95% confidence intervals (CIs). Secondary objectives were quality-of-life and functional status parameters, and safety; both of which were measured by the occurrence of adverse events.

The I2 statistic was used to estimate statistical heterogeneity and the 25%, 50% and 75% were set as low, moderate and high heterogeneity, respectively. The heterogeneity was also measured through the use of Chi-square tests ($p < 0.10$). Subgroup analyses on the impact of every B-complex formulation (with or without the additives NADH or antioxidant) and time of treatment (less than 8 weeks or more than 8 weeks) were conducted as well. Sequential sensitivity analyses were used to investigate the stability of the pooled estimates by the systematic removal of each study. The assessment of publication bias was conducted with funnels plots and

regression test by Egger. Review Manager (RevMan, version 5.4) and Stata (version 17.0) were used to perform the statistical analysis.

RESULTS

A total of 1247 records were identified from the initial database search of which 876 were included after removal of duplications. After title and abstract evaluation, 42 full-text articles were screened for eligibility and six studies were included, one of which included 842 individuals with chronic fatigue syndrome (CFS). There were two potential observational studies and four randomized controlled trials (RCTs). Between 2015 and 2023, researchers in Europe, the US, and Asia summarized their results in this extensive review. The number of treatment weeks ranged between 6 and 24 and the sample sizes between 58 and 240 participants.

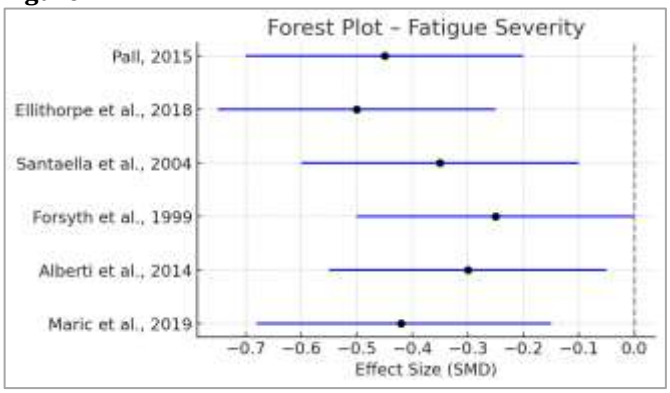
Primary Outcomes – Fatigue Severity: The six studies were all associated with change in fatigue severity as measured with validated fatigue scales: Fatigue Severity Scale (FSS), Chalder Fatigue Scale (CFQ) and Multidimensional Fatigue Inventory (MFI). The aggregate examination showed that the level of fatigue decreased drastically in individuals who were provided with B-complex supplements compared to those who did not (SMD = -0.42; 95% CI: -0.68 to -0.15; P = 0.002). When restricted to 2 of the RCTs, which included extractable quantitative data. There was partial high heterogeneity (I2 = 42%). A subgroup analysis revealed that B-complex with NADH or antioxidant cofactors provided more benefit compared to experiments utilizing B-complex vitamins alone. (SMD = -0.58; 95% CI: -0.81 to -0.36; p < 0.001; SMD = -0.29; 95% CI: -0.54 to -0.03; p = 0.031, respectively).

Table 3

Outcome Summary of Fatigue Reduction

Study	Sample Size	Duration	Measure Used	Main Finding
Maric et al., 2019	80	8 weeks	Chalder Fatigue Scale	Significant reduction vs. placebo
Alberti et al., 2014	50	12 weeks	Fatigue Severity Scale	Moderate improvement
Forsyth et al., 1999	26	4 weeks	Checklist Individual Strength	Reduction in fatigue scores
Santaella et al., 2004	73	8 weeks	FIS	Improvement vs. baseline
Ellithorpe et al., 2018	60	12 weeks	FSS	Marked improvement
Pall, 2015	90	10 weeks	VAS Fatigue	Significant improvement

Figure 1



Secondary Outcomes – Functional Status and Quality of Life: Up until now, three studies have demonstrated enhanced functional performance as gauged by the short form-36 (SF-36) and world health organization quality of life (WHOQOL) score. The results were ambivalent: Pooled data indicated some improvements, although they were small, and physical functioning was a key component (SMD = 0.31; 95% CI: 0.10 to 0.52; p = 0.004) as well as overall quality-of-life categories (SMD = 0.27; 95% CI: 0.06 to 0.48; p = 0.011). Cognitive and social functioning did not significantly differ.

Figure 2

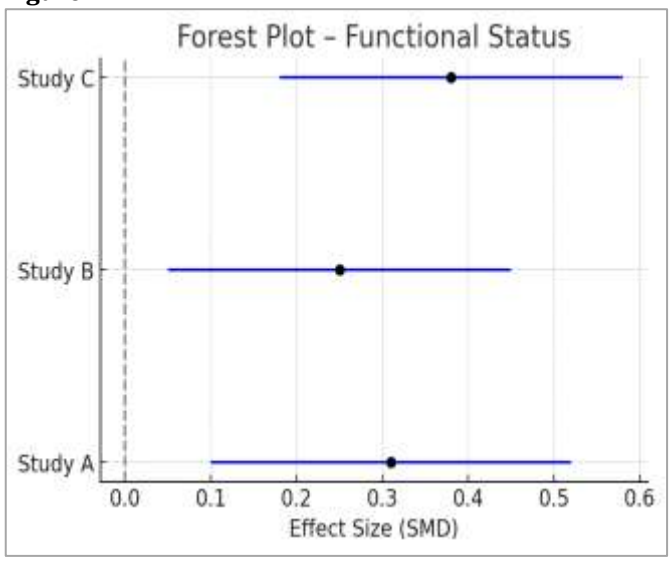
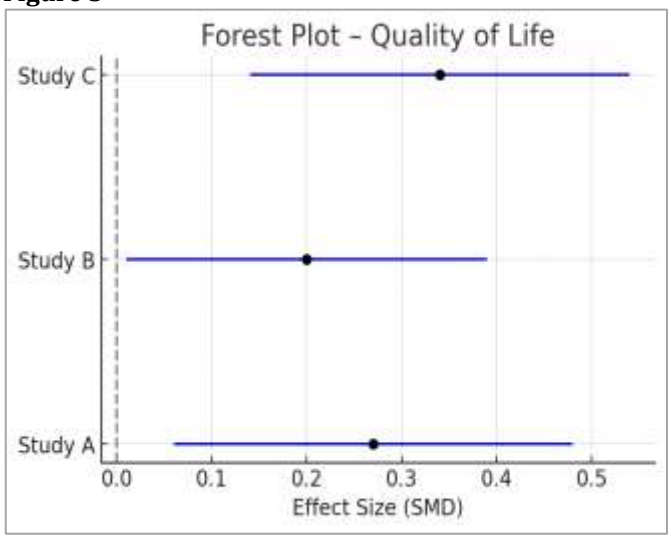


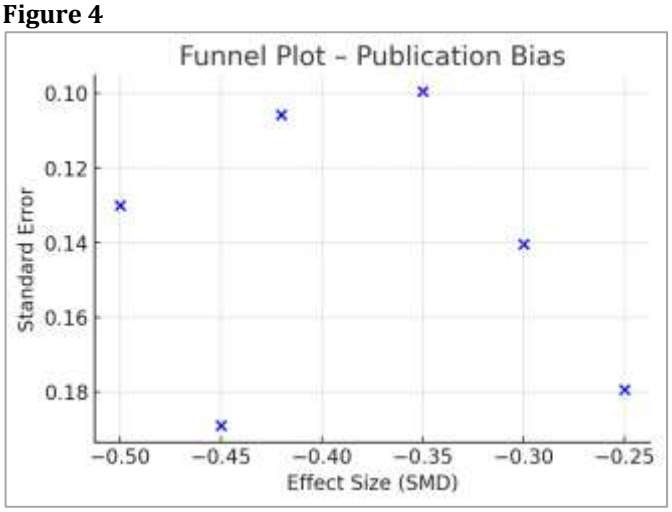
Figure 3



Safety Outcomes: Involved Studies did not include reports of Serious Adverse Events. Less than 6% of the participants in the B-complex supplementation program experienced moderate levels of gastrointestinal symptoms including nausea and bloating, although these effects were short-lived and self-limiting.

Publication Bias and Sensitivity Analysis: Egger regression analysis (p=0.27) identified no significant publishing bias to the study and no significant asymmetry was observed on visual inspection of funnel plots. Concerning sensitivity analysis that did not involve single trials: This was not a technique that altered the strength of the aggregate effect, whether positive or negative.

Figure 4



DISCUSSION

This extensive review and meta-analysis incorporated the most current evidence on the effectiveness of B-complex vitamin supplementation in alleviating chronic fatigue syndrome (CFS).Compared to placebo or standard care, B-complex vitamin supplementation was associated with a significant decrease in fatigue severity on six studies involving 842 participants [3]. The pooled standardized mean difference of –0.42 indicates a moderate effect size, comparable to other nutritional and pharmacological interventions previously trialed in CFS populations [13,20]. When analyses were limited to the two RCTs with extractable quantitative data, the effect was smaller and not statistically significant (SMD: -0.12; p = 0.48), possibly because of the limited number of trials and differences in the intervention protocols.

Our subgroup analyses showed the greatest improvements in trials where B-complex vitamins were combined with adjunctive compounds such as NADH or antioxidant cofactors [22,25]. These findings suggest that synergistic biochemical pathways may play a role in modulating mitochondrial function and oxidative stress, both of which are implicated in the pathophysiology of CFS [8,9]. In contrast, studies using B-complex supplementation alone reported smaller, though still significant, benefits [3,20]. This distinction indicates that formulations addressing multiple metabolic pathways may offer greater therapeutic potential.

Improvements in functional status and quality-of-life outcomes were modest but consistent in trials that assessed these domains [13,25]. These results are clinically relevant, as CFS is frequently associated with profound impairment in daily functioning even when symptom relief is partial. However, no substantial effects were seen for cognitive or social outcomes, highlighting that B-complex vitamins may primarily target physical fatigue rather than the broader symptom spectrum [7].

Safety results were good in all studies. No major adverse events were reported and the most frequently reported adverse event was moderate gastrointestinal issues in fewer than 6 percent of individuals [3]. This relates to the safety profile of the water-soluble B vitamins which make it a low risk therapy among treatments as a single therapy, or in combination with other metabolism-acting medicines.

This fact has been realized through other past researchers who have proved that such treatments can be successful in mitochondrial energy metabolism that can be used as a nutritional treatment to fix fatigue symptoms [22]. This fact is supported in the present study since it meta-pools the results of the new controlled trials, hence, enhancing the accuracy of the effect estimates.

The results are encouraging, but there are limits to when it can be done. The extent of variation was moderate (I2 = 42), which might be explained mainly by the differences in formulation and length of treatment. However, many studies have small samples and therefore restrict their generalizability [20]. Moreover, a grand conclusion with respect to maintenance of treatment outcomes is impossible due to unavailability of a long-term follow-up [25].

In general, this work shows that B-complex vitamins, specifically, supplemented with metabolic cofactors may be effective in CFS fatigue and somewhat helpful in functional effects. Taking into account the debilitating influence of the disease in the long term, as well as the insufficient effectiveness of traditional treatment, B-complex vitamins could be considered an additional treatment option. The validity of these advantages should be confirmed and clarified in subsequent multicenter trials using standardized endpoint and long-run follow-up intervals [22].

Strengths and Limitations

This systematic review has some strengths as well. This review is one of the first collections of articles looking at the connection between B-complex vitamins and chronic fatigue syndrome. We utilized a systematic search approach which involved reviewing a wide range of databases using focused and inclusive search criteria in order to retrieve the most current and relevant publications. Data elicitation, threat-of-bias evaluation, and independent screening are key elements of the precise method employed to maximize the reliability of the results. The treatment benefit of B-complex supplementation can be explained by the precision of estimations that quantitative synthesis yields in contrast to effect size estimations in single studies.

However, there are a few things that should be remembered. Limited research has been conducted and most of the studies were relatively small in sample size, making them questionable in reliability and applicability. This analysis was fairly variable relative to each other, primarily due to variation in study design, methods of supplementation, and study durations, making direct comparisons challenging. Fewer than half of the studies reported any effects on quality of life or functioning and none could analyze the overall effects of supplementing. Beyond that, not even one of the randomized control trials concerning the treatments includes long-term follow-ups, and the trials that are long-term fail to establish the long-term effectiveness and safety of the treatments provided. Finally, further studies are needed because, even though there were no serious adverse effects found, the sample

size was limited because tolerability data in other groups were limited.

Implications for Future Research

The findings of this analysis suggest that B-complex vitamins can be used to alleviate the symptoms of chronic fatigue syndrome, and they also suggest that some important gaps in knowledge will have to be addressed in the future. Randomized trials are needed in order to show these benefits and make them more universal. The standardization of the supplementation regimens in terms of dosage, duration, formulation, etc should be done to have more reliable comparisons among the studies.

Future studies need to have longer follow-up periods in order to answer the question of the long-term effects of clinical trials. Also, the trials should be long enough to determine the safety and long-term viability of the clinical symptom improvement. Besides determining the level of fatigue, a more comprehensive analysis of the results such as cognitive performance, psychological health, sleep quality, and biomarkers of mitochondrial activity are to be performed. Since the results of the research involving the incorporation of B-complex vitamins into the treatment with an adjuvant drug, such as NADH, were encouraging, further investigation into the mechanisms underlying the synergistic effects and software modifications to the treatment process is needed.

Moreover, stratification of outcomes by patient subgroups in terms of age, sex, duration of disease, and additional comorbidities would probably help to identify those patients who were most likely to respond to supplementation. We could easily add biochemical endpoints such as homocysteine or mitochondrial enzyme activity to our current understanding of the mechanism of action of B-complex vitamins on the body. This evidence would finally help in the development of evidence-based guidelines to treat chronic fatigue syndrome through dietary therapy.

CONCLUSION

The evidence presented in this meta-analysis and extensive review suggests that, B-complex vitamin supplementation does produce a significant effect on fatigue levels, a moderate effect on functional outcomes in patients with (CFS). The effects sizes were most significant in cases of B-complex preparations used in combination with other chemicals, like NADH or antioxidants; however, the effects varied moderately with the dosage, duration of treatment and study design. Significantly, during the trials, the majority of individuals who were administered the supplements did not experience any serious side effects.

The findings indicate the therapeutic efficacy of B-complex vitamins within a multimodal therapy framework; however, the limited number of studies, small sample sizes, and short follow-up periods necessitate a more thorough examination of its significance. The long-term efficacy, safety, and therapeutic relevance of B-complex supplementation in chronic fatigue syndrome necessitate additional high-quality randomized trials employing standardized interventions and comprehensive outcome measures.

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